Editorial

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# Sympathetically maintained pain

## Has the emperor no clothes?

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Leriche's report[1] during World War I that periarterial sympathectomy relieves pain in soldiers with nerve injury popularized the hypothesis that sympathetic efferent activity in some way augments chronic pain, and launched a series of sympathoablative treatments that remain in common use today. United States physicians carry out approximately 43,000 sympathetic nerve blocks per year for the treatment of pain.[2] Blocks that result in pain relief prompt more permanent interruption of the sympathetic chain by surgery, by injection of neurolytic agents, or by thermocoagulation. The diagnosis in most of these patients is reflex sympathetic dystrophy (RSD), more recently termed complex regional pain syndrome (CRPS) type I, consisting of pain, allodynia, or hyperalgesia disproportionate to the inciting injury and edema, changes in skin blood flow, or abnormal sudomotor activity in the painful region; or causalgia caused by a peripheral nerve injury, now termed CRPS type II.[3]

The rationale for sympathoablative treatments was strengthened in the 1980s by animal studies showing that sympathetic efferent activity may augment pain in models of both nerve injury and inflammation, and that anatomic changes, such as increased densities of axonal adrenergic receptors or sympathetic fiber sprouting into dorsal root ganglia, may underlie sympathetically maintained pain after nerve injury.[4]

As the field of pain research has matured, there have been critiques of the "sympathetic hypothesis." Raja et al.[5] pointed out that only some patients with nerve injury or RSD respond to sympathetic nerve blockade, and they proposed that patients' pain be defined as "sympathetically maintained" or "sympathetically independent" according to their response to temporary sympathetic nerve block. They also criticized local anesthetic blocks of the sympathetic ganglion as being invasive, difficult to blind, and confounded by a large placebo response and by the systemic effects of lidocaine, which inhibits ectopic sodium currents at nerve injury sites. They proposed an alternative procedure: systemic infusion of the alpha-adrenergic antagonist phentolamine,[5] which can be more readily blinded and whose results appeared to correlate well with results of lidocaine ganglion blocks.

These modest revisions were not enough for more radical skeptics such as Geoffrey Schott[6] and Jose Ochoa (see Verdugo et al.[7]), who have argued that the apparently beneficial effects of any type of sympathetic ablation result either from a placebo effect or from interrupting visceral primary afferent fibers that run with some sympathetic nerves.[6] A controlled study[7] compared IV phentolamine with IV phenylephrine (an alpha-1 adrenergic agonist that should increase sympathetically maintained pain) in 29 patients with causalgia, polyneuropathy, or RSD and found no difference in pain resulting from the two oppositely directed sympathetic interventions. A comparison of IV phentolamine with placebo and with epidural lidocaine-fentanyl in 37 patients with failed back surgery found only one phentolamine responder.[8] A study of lidocaine versus saline sympathetic ganglion blocks in patients with CRPS type I showed that a saline block produced an average of 20 hours of nearly complete relief,[9] which should give pause to clinicians who proceed to permanent sympathetic ablation after several successful temporary local anesthetic blocks. Recent meta-analyses of studies of sympathetic ablation found little evidence of efficacy.[10] There are additional problems with long-term sympathoablative treatments; systemic drugs such as doxasozin or phenoxybenzamine are poorly tolerated because of postural hypotension, whereas neurolytic sympathectomy may cause neuralgias, and the mean duration of effect is only 6 months.[11]

The attempted demolition of the sympathetic hypothesis has generated thoughtful responses. Raja et al. have refined the phentolamine method by showing that it takes higher doses than they (and Verdugo et al.) originally used.[12] Raja et al. have also developed easily blinded pain-provocative proce-

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dures. Injection of adrenergic agonists near an amputation stump neuroma[13] or into hyperalgesic skin in CRPS type I increased pain.[14] A double-blind study showed that infiltration of phenylephrine or epinephrine into skin affected by postherpetic neuralgia exacerbated pain compared with saline.

Positive data from recent clinical experiments, as well as most of the animal data on sympathetically maintained pain, are limited to cases with peripheral nerve lesions, which represent a minority of the cases in which sympathetic blocks are used in the clinic. For this reason, great interest was recently aroused by three independent reports (including one from our group) that the pain and mechanical hyperalgesia caused by the application of strong capsaicin preparations to the skin of normal volunteers was increased by adrenergic agonists[16] and decreased by systemic[17] or local administration of phentolamine.[18] Capsaicin, the pungent ingredient in chili peppers, is a favorite experimental stimulus among pain researchers because its initial application causes massive discharge of peripheral pain nociceptors that carry vanilloid receptors and temporarily sensitize both peripheral and central sensory neurons. These three reports suggested that this ability of capsaicin to produce sympathetically modulated pain in most human subjects supports the plausibility of a sympathetic component to chronic pain and provides a model in which the specific mechanisms of this interaction might be worked out. In the face of the claim by Ochoa's group and by Schott that the emperor had no clothes, this finding provided a vestige of modesty.

Alas, Baron et al.[19] strip that fig leaf away with their elegant study reported in this issue of *Neurology*. As in the previous studies, they produced pain and allodynia by applying capsaicin to the forearm skin of normal volunteers. Instead of pharmacologic modulators of sympathetic neurotransmission, they used natural stimulation of the subjects' sympathetic system by heating or cooling with a thermal suit. Marked increases and decreases in sympathetic efferent activity were confirmed by measurements of skin blood flow and temperature in the index finger of the capsaicin-treated arm, but no changes in spontaneous pain or hyperalgesia occurred in the capsaicin-treated area. These results, based on maximum natural stimulation of the subjects' own sympathetic system, refute those based on pharmacologic manipulations. The contradiction between the current results and the three positive capsaicin studies raises concerns about the validity of the pharmacologic tests in the capsaicin model and in patients. At the concentrations reached, adrenergic agonists may have pain-promoting actions, and phentolamine may have pain-relieving actions that go beyond excitation or blockade of adrenergic receptors.

It would be a mistake to abandon the sympathetic pain hypothesis on the basis of a few negative trials just when less toxic ablative interventions, such as biological regulation of adrenergic receptors or subperspecific adrenergic antagonists, may be within reach. Investigators not as invested in the current polemic should examine whether there is a specific response to sympathetic block in patients with nerve lesions or CRPS type I, reported to be rare or nonexistent by Verdugo et al.[7] Randomized, double-blind controls with multiple provocative and inhibitory tests should be used, including natural perturbations of the sympathetic system as illustrated by Baron et al.,[19] and correlated with the long-term outcomes of treatments that modify sympathetic activity.

If neurologists are unable to enter patients into controlled clinical trials, should they still use sympathoablative treatments on patients with nerve injury or CRPS type I? In fairness to the advocates of sympathetic blockade, a large proportion of accepted surgical and regional anesthetic procedures have not been validated by randomized trials. No one questions the observation that stellate ganglion or lumbar sympathetic blocks often have powerful pain-relieving effects that far outlast the expected 6- to 12-hour effect of the local anesthetic. Such relief often makes possible vigorous physical therapy, a key component in rehabilitation of the pain patient. Whether pain relief is due to sympathetic blockade, placebo, or spillover of anesthetic onto somatic nerves does not matter unless one tries to infer whether a permanent ablation of the sympathetic chain is indicated. The current critique (reviewed above) raises concerns about the benefit–risk ratio of permanent sympathetic ablation, and about how one might identify patients likely to get pain relief from the more invasive procedures. Response to several high-dose phentolamine infusions compared with placebo under double-blind conditions appears to be the best available criterion until additional diagnostic tests, including sympathetic augmentations, have been better validated, although the caveats of Baron et al. about the possible nonspecific effects of phentolamine remain worrisome.[19]

Sympathetically maintained pain was once a reigning hypothesis in pain research, but does the emperor now have no clothes? On his recent visits to the clinic, we think he looked pretty close to naked, but that is because sartorial standards have been rising. More human studies with the rigor exemplified by Baron et al. may give him what he lacks—perhaps even a hot and cold running water suit.

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# Restless legs syndrome

## A disease in search of identity

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Restless legs syndrome (RLS) is not rare but is rarely diagnosed by clinicians. Articles published in this and recent issues of *Neurology* reflect the growing interest in this area, fueled by new findings from pharmacologic, electrophysiologic, and neuroimaging studies. Despite a lucid description over 50 years ago by Ekbom,[1] there is considerable misconception about RLS. Persons with RLS, even when their symptoms are quite troublesome or disabling, often do not seek medical attention, or the symptoms are wrongly attributed by physicians to nervousness, insomnia, stress, muscle cramps, arthritis, or a simple consequence of aging. Although no medical specialty has claimed rights of ownership to RLS, the correct diagnosis is usually made by neurologists, movement disorder experts, and sleep specialists.

The poor recognition and frequent misdiagnosis have hampered epidemiologic studies in RLS. Estimated prevalence rates vary widely, from 1% to 15%, but the true prevalence is probably close to 5% in the general population and considerably higher in the elderly. One study of 133 patients with typical RLS found the mean age at onset to be 27.2 years and the presence of RLS in at least one first-degree relative in 63% of cases.[2] Future epidemiologic studies will be aided by the diagnostic criteria formulated by the International Restless Legs Syndrome Study Group (IRLSSG).[3] The minimal criteria include the following: 1) an intense, irresistible urge to move the legs, usually associated with sensory complaints (paresthesia or dysesthesia); 2) motor restlessness; 3) worsening of symptoms at rest and relief with motor activation; and 4) increased severity in the evening or at night. Periodic limb movements in sleep (PLMS), detected by an overnight sleep study and present in at least 80% of patients with RLS, is the

**See also pages 932, 938, 944, 1060, and 1064**

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